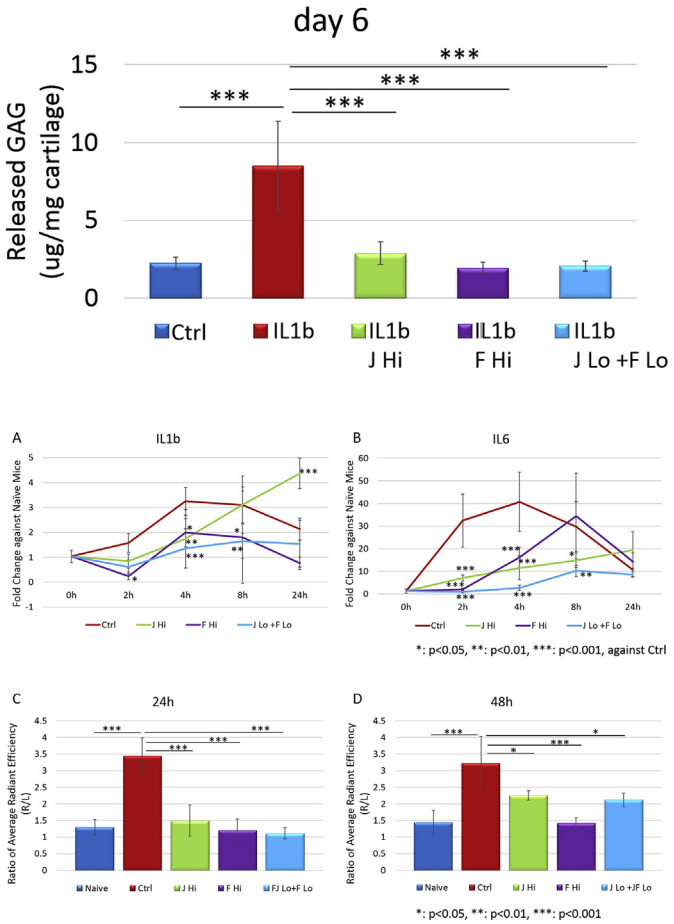

660
SYNTHESIS AND CHARACTERIZATION OF GOLD NANOPARTICLES COMBINED WITH CURCUMIN AND ITS EFFECT ON EXPERIMENTAL OSTEOARTHRITIS IN MICE

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Purpose: The aim of study was the synthesis and characterization of a system combining gold nanoparticles (AuNPs) to curcumin and evaluate its therapeutic potential in an experimental model of osteoarthritis (OA) in mice by destabilization of the medial meniscus (DMM).
Methods: Thirty two C57BL6 strain male mice, 8 weeks of age, were used. For the experimental induction of osteoarthritis we used DMM destabilization technique proposed by Glasson et al. (2007). For the synthesis of AuNPs we used the hydrochloride polyallylamine (PAH) as a stabilizer and sodium borohydride as a reducer agent and characterizations were performed by UV-VIS spectroscopy, dynamic light scattering (DLS) and determination zeta potential. Four groups were formed, each with eight animals, named as A (360 μg of AUNP-PAH), B (20 μg of curcumin), C (360μg of AUNP-PAH-Curcumin) and D (sham) thus distributed in accordance with the administered therapy. All animals were treated with three applications by intra-articular injection, every 15 days, with the beginning of the treatment was given on day 14 after induction of OA. After 6 weeks of induction of OA, the animals were euthanized. All knee joint (KJ) were fixed in 10% buffered formalin for 24 hours and decalcified in EDTA solution monosodium 15% for two weeks. They were then processed according to routine procedures and the slides stained with hematoxylin and eosin (H&E) and Safranin O fast green to evaluate the concentration of proteoglycans. These were assessed by 2 independent observers in a blind study, using the criteria established by Mankin et al. (1971). By which a score of each joint was obtained by calculating the formula, standardized by the evaluation system of Osteoarthritis Research Society International (OARSI), and established by Bao et al. (2009) and Rutgers et al. (2010), thus, each KJ received a score ranging from 0 to 24. Data were analyzed for normal distribution using the Kolmogorov-Smirnov test. Therefore, normal data were submitted to analysis of variance, and, in cases of significance, means were compared using the Tukey test. For all statistical analysis was adopted the 5% significance level.
Results: Histological analyzes showed a clear distinction of articular cartilage damage among the different groups. Focal discontinuity of cartilage surface area and erosion with loss of surface lesions were found more often in groups A (360 μg of AUNP-PAH) and B (20 μg of curcumin), and loss of proteoglycans, as evidenced by decreased safranin O staining fast green. KJ in group C (360μg of AUNP-PAH-Curcumin), there was edema and fibrillation of the cartilage surface were the most frequent changes, emphasizing greater dial proteoglycans. While in the D (sham) group, there were injuries such as microfractures with presence of fibrocartilage, remodeling and bone repair. With regard to the mean values score, there was a greater value in group D KJ, with a mean score of 18.25. In addition, there was significant difference (p 0.05) between these groups. C group animals showed a significant decrease ($p < 0.001$) in their scoring average values in the control group, however there was no statistical difference with the other groups.
Conclusions: The results show the importance of the study and development of new nanodrugs. Despite the solutions studied have shown similarity to each other, one should consider that animals treated with the solution of AUNP-PAH-Curcumin, presented less severe in the histological lesions. Further studies evaluating the expression of antiinflammatory genes and pro-inflammatory, catabolic and anabolic mediators are needed to demonstrate the effective role of this therapeutic option in the treatment of OA.

661
THE EFFECTS OF SIMVASTATIN ON THE SYMPTOMS OF KNEE OSTEOARTHRITIS(KOA) DURING A 3-MONTH TREATMENT COURSE IN A SAMPLE OF IRAQI PATIENTS

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Purpose: Osteoarthritis is the most common form of arthropathy. Matrix metalloproteinases (MMPs) and proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-a) play an important role in this condition. Statins show non lipid modefiable effects, pleiotropic effects, which could be responsible for their anti oxidative and anti inflammatory effect.
Methods: One hundred thirty (130) patients were randomly assigned to receive oral simvastatin 20 mg once daily in (group A =n 62), or placebo (group B =n 68). The efficacy outcome measure was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) including the pain, stiffness and physical function subscales.
Results: The mean pain score at first visit (baseline) was (8.6±2.2) in group A, vs. (6.98±2.2) in group B, $P<0.001$. At the second visit after one month the pain scores in both groups were lowered down. Two month later the pain score in group A decreased more while in group B was slightly increased. After three month Pain score in group A continued to decrease (5.14±2.9), while in group B there was a smaller change than baseline with a mean difference of only (0.6 ± 0.57). The comparison in mean differences of the baseline score vs. the last visit (after three month) showed a significantly higher change of pain score in group A than in group B. The same trends had been observed in scales of stiffness, physical function and total WOMAC, and the mean changes in WOMAC scales in group A than group B.
Conclusions: The findings of this study indicate that simvastatin at the oral once-daily dosage of 20 mg is more effective than placebo in treating knee OA symptoms.

662
DO PHYSICIANS TREAT OSTEOARTHRITIS PROPERLY IN CHINA: ANALYSIS OF 67382 OUT-PATIENTS FROM PEKING UNIVERSITY PEOPLE'S HOSPITAL

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Purpose: There is a high prevalence of osteoarthritis(OA) in old population, and physicans usually treat OA based on the guideline recommended by OARSI. Until now, there is no report about the treatment in

China. In this study, we aim to analysis the treatment of OA in China and its Rationality.

Methods: The study enrolled all out-patients prescriptions for the treatment of osteoarthritis in Peking University People's Hospital in 2012. Statistical method was applied to analyze the characters of the treatment for OA, and the differences of the choice of medications caused by different clinical departments.

Results: A total of 67382 prescriptions involving 25410 osteoarthritis out- patients were enrolled in this study. The incidence of OA- related visits to the hospital was 2.6 times per year per person. 51 medications were given, categorized into 8 groups according to 2008 OARSI hip and knee osteoarthritis recommendations: ①topical NSAIDs and capsaicin; ②acetaminophen; ③NSAIDs; ④weak opioids; ⑤intra-articular(IA) injections; ⑥glucosamine; ⑦anti-osteoporosis drugs;⑧traditional Chinese medicine(TCM). As many as 23 species of TCM were involved, seconded by anti-osteoporosis drugs(9 species). Among all the drugs, TCM was the most commonly prescribed(61.3%), seconded by glucosamine(50.6%). The study mainly involved rheumatology department, orthopedics department, pain management department, and department of traditional Chinese medicine. Different specialists prescribed differently, while rheumatologists may prefer NSAIDs(24.6%) and glucosamine(78.9%) more, orthopedics prefer NSAIDs(28.3%), glucosamine(60.4%) and TCM(66.1%), doctors from pain management department may give more weak opioids(17.7%), glucosamine(60.4%) and IA agents(86.2%), and traditional Chinese doctors mainly prescribe traditional Chinese medicine(90.3%). 83.3% of all prescriptions include oral medications, 41.5% include topical agent. Rheumatologists and orthopedics give more oral medications, doctors from pain management department prefer IA agents. Doctors from traditional Chinese medicine department use more topical agent.

Conclusions: Physicians in China prefer to use glucosamine and traditional Chinese medicine to treat OA, which is lack of clear guidelines. Compared with the physicians from the traditional Chinese medine department and the pain management department, rheumatologists and orthopedics treatment OA based on guidelines more.

Therapy: Biological

663

PHASE 1 STUDIES OF ANTI-INTERLEUKIN-1 DUAL-VARIABLE DOMAIN IMMUNOGLOBULIN IN HEALTHY SUBJECTS AND PATIENTS WITH OSTEOARTHRITIS

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Purpose: Interleukin (IL)-1 is a potent catabolic cytokine that plays an important role in the pathogenesis and progression of osteoarthritis (OA). Preclinical proof of concept for simultaneous inhibition of IL-1α and IL-1β was demonstrated by both cartilage protection and increased tolerance to mechanical nociceptive pain. Two phase 1 clinical trials investigated the use of a novel human dual-variable domain–immunoglobulin (DVD-Ig™) simultaneously targeting IL-1α and IL-1β (ABT-981).

Methods: ABT-981 was evaluated in a randomized, double-blind, single ascending dose (SAD), placebo-controlled trial in 56 healthy subjects and in a randomized, double-blind, multiple ascending dose (MAD), placebo-controlled trial in 36 patients with mild to moderate knee OA (NCT01668511). In the SAD trial, each cohort received a single intravenous (IV) or subcutaneous (SC) dose of ABT-981 (0.3, 1, 3, and 10 mg/kg IV or 0.3, 1, and 3 mg/kg SC) or placebo in a 6:2 ratio. In the MAD trial, cohorts 1-3 received ABT-981 (0.3, 1, or 3 mg/kg) or placebo in a 7:2 ratio every 2 weeks (EOW) for 4 SC injections total, and cohort 4 received ABT-981 (3 mg/kg) or placebo in a 7:2 ratio every 4 weeks (E4W) for 3 SC injections total. Safety, tolerability, pharmacokinetics (PK), anti-drug antibodies (ADAs), and biomarkers were assessed through day 85 in the SAD trial and through day 113 for the first 3 cohorts and through day 127 for the fourth cohort in the MAD trial. In the MAD trial, a panel of serum/urine biomarkers of target engagement, inflammation and joint degradation were compared between ABT-981-treated and placebo groups from day 1 to 57.

Results: The incidence of adverse events (AEs) was similar with single-dose ABT-981 vs placebo via IV (66.7% vs 50.0%) or SC (55.6% vs 66.7%) routes and with multiple SC doses of ABT-981 vs placebo (53.6% vs 62.5%). The majority of AEs were mild or moderate and considered not or probably not related to study drug. The most common AE with ABT-981 vs placebo was diarrhea via IV (20.8% vs 12.5%) and headache via SC (22.2% vs 0%) in the SAD trial, and injection-site reaction (17.9% vs 0%) in the MAD trial. No infusion reactions or injection-site reactions occurred in the SAD trial. In the MAD trial, absolute neutrophil count (ANC) decreased dose-dependently with ABT-981 dosing, starting at 48 hours and reaching nadir by 14 days, with lowest ANC values (2.1-2.3/mm^3) observed with 3 mg/kg. Only 1 patient had a transient grade 2 neutropenia after 1 dose in the 3 mg/kg EOW group, which was considered possibly study-drug related, along with a serious AE of grade 3 bronchitis/viral syndrome that was also considered possibly study-drug related. ABT-981 Cmax and AUC increased in a dose-proportional manner after single doses of 0.3-10 mg/kg IV or 0.3-3 mg/kg SC and multiple doses of 0.3-3 mg/kg SC EOW. Estimated relative bioavailability after SC administration was 46%. Following EOW dosing, accumulation in AUCτ was approximately 2-fold. Mean terminal half-life ranged from 10-13 days. No apparent ADA effect on ABT-981 PK was observed. In the MAD trial, ABT-981 at all 3 doses significantly reduced serum levels of high-sensitivity C-reactive protein (hsCRP; $P<0.05$), matrix metalloproteinase (MMP)-degraded type 1 collagen (C1M; $P<0.05$ at 1 and 3 mg/kg), IL-1α ($P<0.001$; **Figure**), and IL-1β ($P<0.001$; **Figure**). Serum concentrations of MMP-degraded type 3 collagen (C3M; 1 and 3 mg/kg) and MMP-degraded CRP (CRPM; 3 mg/kg) demonstrated decreasing trends ($0.05<P<0.1$) with ABT-981 treatment but did not reach statistical significance. These trends suggest that ABT-981 engaged with IL-1α and IL-1β targets and elicited an anti-inflammatory response in patients with knee OA.

Conclusions: The results of these phase 1 trials demonstrate that ABT-981 was well tolerated and had dose-proportional PK in healthy subjects and patients with knee OA. The similar safety profiles between ABT-981 and placebo support phase 2 investigation of ABT-981 in